**ORIGINAL RESEARCH**

# Role of magnetic resonance imaging in evaluating post-covid-19 patients with rhino-orbito-cerebralmucormycosis: A study of 72 patients

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**ABSTRACT**

**Introduction:** Patients with COVID-19 pneumonia are predisposed to fungal infections due to alteration of cell mediated immunity and over expression of inflammatory cytokines. Other predisposing factors include diabetes mellitus, aggressive use of systemic steroids, and other such immunosuppressive conditions. Contrast enhanced Magnetic Resonance Imaging (CE-MRI) serve as important imaging modality to assess the extent of involvement and to look for complications, if any, which are quite common.**Objectives:** The objective of the present study was to describe the myriad of imaging findings in Rhino Orbital Cerebral Mucormycosis (ROCM) in Post covid-19 patients and an attempt to stage the disease.**Materials and Methods:** We conducted a cross sectional study on 72 patients with ROCM from May 2021 to August 2021,who were subjected to a CE-MRI of the paranasal sinuses and orbit. The clinical and radiographic data were collected and analysed. **Results:** Among Covid-19 infected patients, mucormycosis affected more frequently the patients with predisposing conditions like diabetes (47 patients ~65%) followed by other immuno-compromised conditions. On MRI most patients (72.2%), were found to have stage 3 disease and maxillary sinus is the most frequently involved sinus. Orbital involvement is the most common involved extra sinus site followed by intracranial extension and skull base osteomyelitis. Most frequent intracranial complication was meningitis.**Conclusion:** MRI plays an important role in evaluating the extent of disease, various complications, and pathologies to be searched in a case of ROCM. COVID19 associated mucormycosis shows a frequent spread of infection to extra sinus sites and is associated especially with uncontrolled diabetes, steroid administration and oxygen supplementation. Hence, imaging plays a vital role in assessing the extent of the disease, its aggressive to management and timely intervention and thus helps in reducing the morbidity and mortality of patients.

**Key words:**Mucormycosis, ROCM-rhino-orbito-cerebral mucormycosis, Covid-19, paranasal sinuses, magnetic resonance imaging, RT-PCR



## INTRODUCTION

The COVID-19 disease, which primarily affects the respiratory system, and affects almost every organ in the human body is found to be associated with a wide range of bacterial and fungal co-infections. With the advent of the novel coronavirus and more than 3 crore confirmed cases in India by August 2021, there was a concomitant increase in the fungal co-infections.[1] Of particular significance is Rhino Orbital Cerebral Mucormycosis (ROCM), a life threatening infection caused by saprophytic fungi belonging to the genera Mucor, Rhizopus and Absidia. They belong to the order Mucorales and zygomycetes.[2] This disease which originates in the sinonasal mucosa, rapidly invades its neighbouring structures including the orbit and the brain. ROCM is associated with a high residual morbidity due to the angioinvasive nature of the disease.[3]

In the pre-Covid era, the annual prevalence of mucormycosis globally was around 10,000 barring India. The estimate rose to 910,000 cases after the inclusion of Indian data. The cumulative burden of Mucormycosis ranged from 1.4 to 2.1 lakh cases a year with a prevalence of 14 cases per 1 lakh individuals and mean attributable death of 65,500 deaths per year in India alone.[4]

In the Covid era, India reported more than 40,000 cases in a span of three months (May to July 2021).[5]

There has been a surge of Mucormycosis cases post Covid due to exorbitant use of systemic steroids, increased serum free iron, industrial oxygen, use of iron and zinc for the management of covid-19, reusable oxygen humidifiers and overzealous use of steam inhalation.[6]

Hence, imaging plays a vital role in assessing the extent of the disease, its aggressive to management and timely intervention.

Our objective was to identify and study the various imaging findings in patients with ROCM using contrast enhanced magnetic resonance imaging.

## MATERIALS AND METHODS

### PATIENT SELECTION

We conducted a hospital based cross sectional study in a tertiary care centre of South India on the role of MRI in evaluating post Covid-19 patients presenting with ROCM from May 2021 to August 2021. Approval from the Institutional ethics review committee was obtained. We included patients of all age groups and both genders diagnosed as having COVID-19 pneumonia after a nasopharyngeal RT-PCR swab test, or a High Resolution Computed Tomography (HRCT) Chest scan.

After obtaining informed and written consent from each patient, we evaluated a total of 120 patients referred to the Department of Radiodiagnosis for MRI scan from the Out-patient and In-patient Departments of Medicine, ENT, Ophthalmology and Neurology. The patients were subjected to either a KOH mount or biopsy or both to know the microbiological diagnosis. 24 patients were excluded as they did not reveal Mucor in the culture, or revealed other fungi or bacteria. 8 patients were lost to follow up and had to be excluded. 6 patients who had undergone prior surgery of the sino-nasal region were also excluded from the study. Contrast could not be done in 5 patients and were excluded from the study. MRI could not be performed in 3 patients as they had a pace-maker *in situ*.

The procedures followed were in accordance with the ethical standards of the Institutional committee on human experimentation and with the Helsinki Declaration of 1975 that was revised in 2000.

### IMAGING TECHNIQUE

A CE-MRI of the Paranasal sinuses and orbits was performed using SIEMENS MagnetomAvanto 1.5 Tesla MRI machine (Siemens medical systems. Erlangen, Germany). Axial and coronal T1W (TR/TE-550/13) and T2W (TR/TE-3860/84) Spin Echo images with and without Fat saturation (inter-slice gap-1.1mm; slice thickness-3 mm), Axial 3D Constructive Interference in Steady State (3D-CISS) (TR/TE-1200/208,slice thickness-1mm) axial Diffusion Weighted Images (DWI) (b values 0, 500 and 1000) with Apparent Diffusion Co-efficient (ADC) maps and axial Susceptibility Weighted images (SWI) images (TR/TE-49/40, flip angle-15, interslice gap-1.1mm, thickness-3mm) were obtained.

Contrast study was done with Gadopentetatedimeglumine(0.1mmol/kg body weight). Post Gadolinium-axial and coronal T1 with fat saturation, and axial Volumetric Interpolated Breathhold Examination (VIBE) (TR/TE-9/2.38, flip angle 10) images were obtained.

The planning of the axial slices was done on the sagittal plane. The position block was angled parallel to the hard palate. The positioning block in the other two planes were checked (perpendicular to the nasal septum on coronal plane). Slices were covered from the superior border of the frontal sinus to the level of lower lip with an Field of View (FOV) of 160-180mm.

The planning of the coronal slices was done on the sagittal plane. The position block was angled perpendicular to the hard palate. The positioning block in the other two planes were checked (perpendicular to the nasal septum on the axial plane). Slices were covered from the tip of the nose to the brainstem with an FOV of 160-180mm.

### IMAGE ANALYSIS

Appearance on plain T1 and T2W images, type of post contrast enhancement of mucosa of involved sinuses, involvement of extra sinus structures like orbit, face, intracranial extension and complications like abscesses cerebritis, meningitis, infarcts, involvement of cranial nerves, cavernous sinus thrombosis, arterial thrombosis, skull base osteomyelitis were noted.

Involvement of retroantral, masticator space, pterygo-palatine fossa is evidenced by fat stranding and soft tissue extension similar to appearance of intra-sinus soft tissue. Orbital cellulitis was seen as fat stranding in retro-orbital fat without abscess formation.

Evaluation of intracranial extension is evidenced by enhancement of meninges, presence of extradural collections, ischemic infarcts, cerebritis and intra-cerebral abscess. Involvement of cavernous sinus and arteries is evidenced by non-enhancement on post contrast studies.

Patients in the study were divided into three groups according to classification suggested by Rupa et al, based on extent of regional involvement as described below [7].

**Table 1**

| Stage | Areas involved |
|---|---|
| Stage 1 | Nose and paranasal sinuses. |
| Stage 2 | Paranasal sinuses with immediate adjacent areas which are surgically resectable with minimal morbidity.<br>Eg. Extraconal compartment of orbit, palate, oral cavity. |
| Stage 3 | Intracranial extension(Intra cerebral or extradural) or areas which are partially resectable with extension to pterygopalatine fossa, cavernous sinus, cheek and periorbital region. |

**STATISTICAL ANALYSIS**

The data collected was analysed by descriptive studies such as mean, median, standard deviation, proportions and graphs for continuous parameters and absolute and relative frequencies was calculated for categorical variables.

Chi-square test was performed on grouped continuous variables.

Data was entered in Microsoft excel and analyzed by SPSS version 24.0.

**RESULTS**

**Table 2: Demographics**

| Total number of patients-72 | |
|---|---|
| Mean Age. | 46.5 (Range-13-80years) |
| Male: Female. | 52:20 |
| Diabetes mellitus. | 47 |
| Steroid treatment. | 7 |
| Oxygen dependent status. | 6 |
| Other comorbidities:<br>Chronic kidney disease<br>Hypertension | <br>4<br>22 |

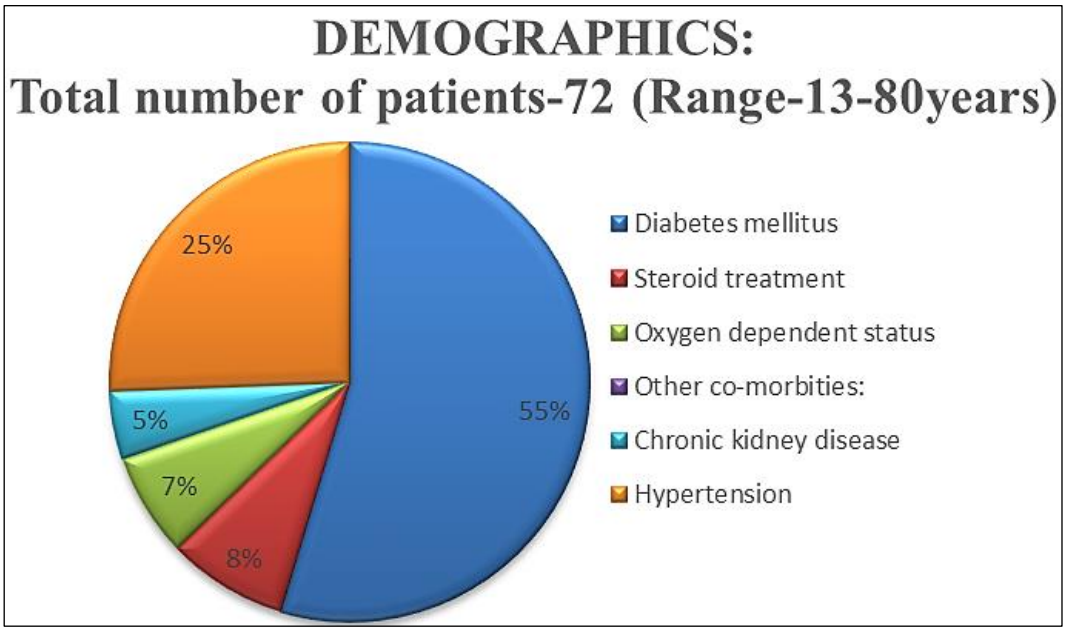



**Fig 1: Pie chart showing Demographics**

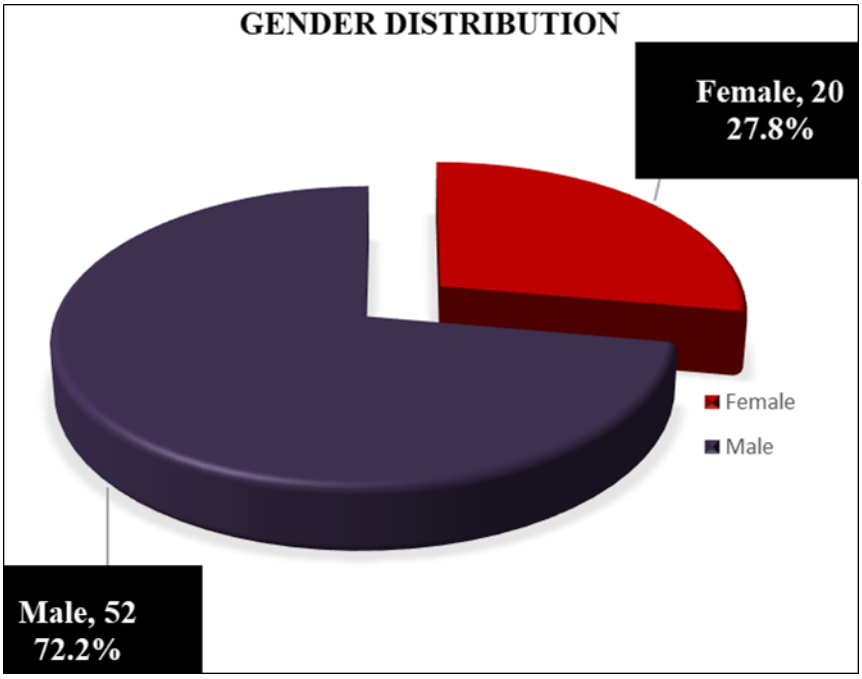



**Fig 2: Pie chart showing age distribution**

A total of 72 histopathologically confirmed rhino-cerebral mucor-mycosis cases underwent contrast MRI.

**Table 3:Staging based on extent of regional involvement**[7]

| Stage | Areas involved | Number (%) |
|---|---|---|
| Stage 1 | Nose and paranasal sinuses. | 6[8.3%] |
| Stage 2 | Paranasal sinuses with immediate adjacent areas which are surgically resectable with minimal morbidity.<br>E.g. Extraconal compartment of orbit, palate, oral cavity. | 14[19%] |
| Stage 3 | Intracranial extension(Intra cerebral or extradural) or areas which are partially resectable with extension to pterygopalatine fossa, cavernous sinus, cheek and periorbital region. | 52[72.2%] |

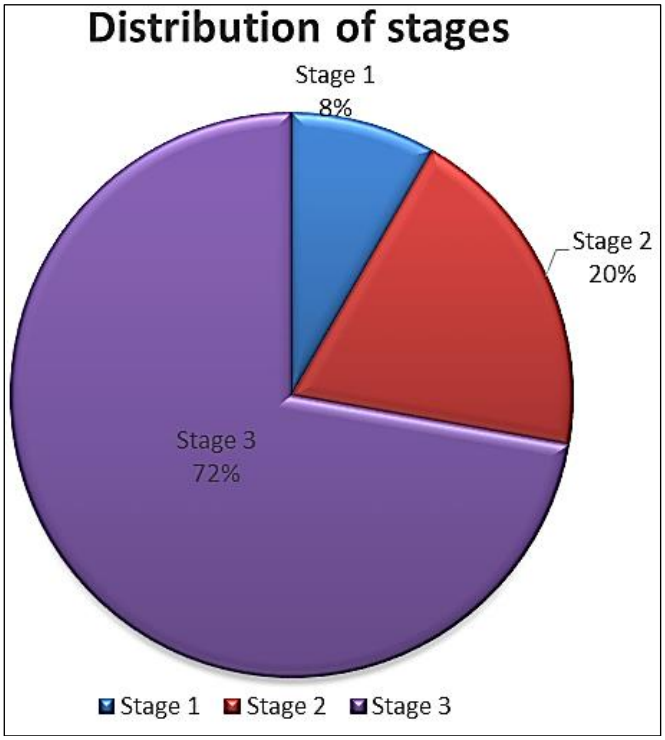



**Fig 3: Pie chart showing distribution of stages based on extent of regional involvement**

**Table 4: Frequency of involvement of sinuses**

| Sinuses involved | Number of patients (%) |
|---|---|
| Maxillary sinus | 69 |
| Ethmoid sinus | 62 |
| Frontal sinus | 47 |
| Sphenoid sinus | 56 |

**Table 5: Complications**

| Complication | Number | Percent |
|---|---|---|
| Orbit involvement | 46 | 63% |
| Intracranial extension | 30 | 41% |
| Skull base osteomyelitis | 6 | 8% |

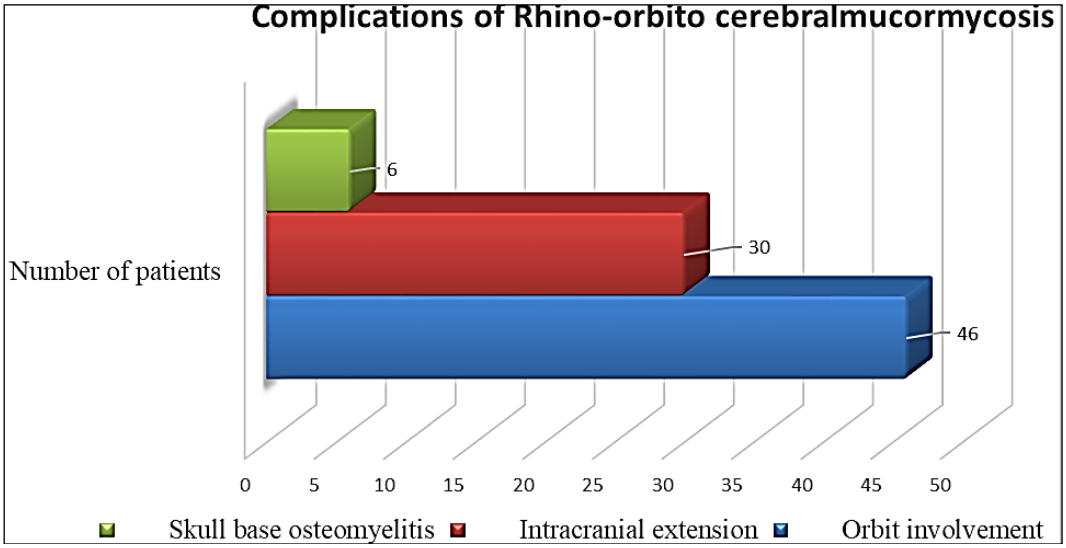



**Fig4: Pie chart showing distribution of complications**

**Table6: Spectrum of findings in cases of orbital involvement**

| Findings | Number of patients | Percent |
|---|---|---|
| Optic nerve involvement | 23 | 31% |
| Extra-ocular muscle involvement | 19 | 26% |
| Globe abnormality | 5 | 6% |
| Orbital apex involvement | 2 | 2% |
| Pre-septal cellulitis | 8 | 11% |

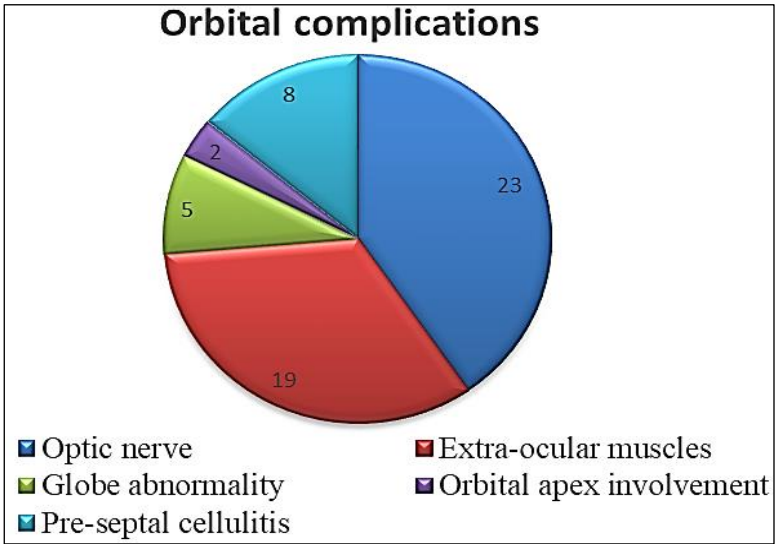



**Fig 5: Pie showing intra orbital complications**

**Table 7: Intracranial Complications**

| Intracranial complication | Number of patients |
|---|---|
| Cerebral abscesses | 8 |
| Cerebritis | 4 |
| Meningitis | 17 |
| Infarcts | 14 |
| Cranial nerves involved | 3 |
| Cavernous sinus thrombosis | 10 |
| Internal carotid artery thrombosis | 9 |
| Skull base osteomyelitis | 6 |

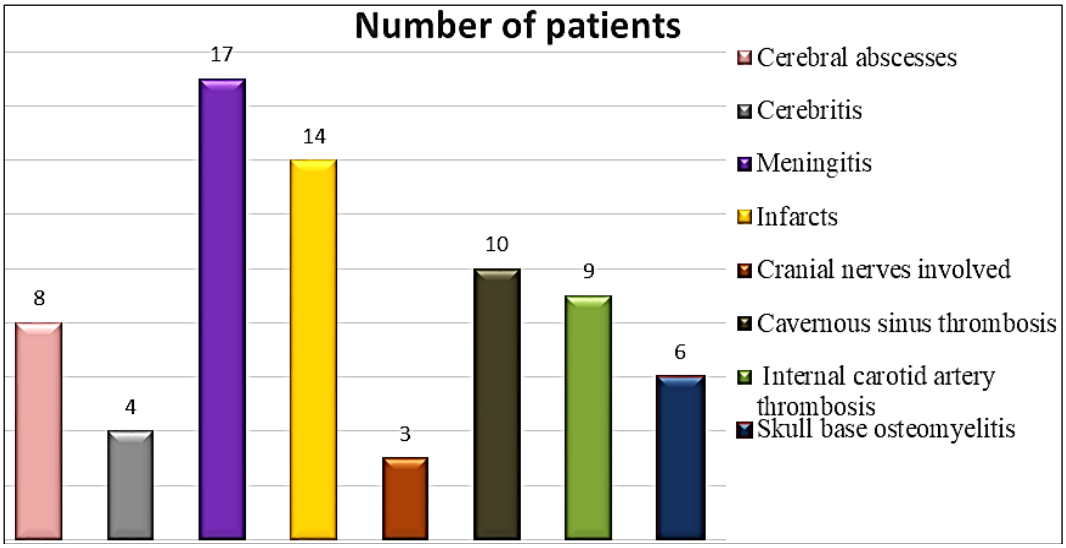



**Fig 6: Bar chart showing intracranial complications**

**IMAGE GALLERY:**
**Case 01:**

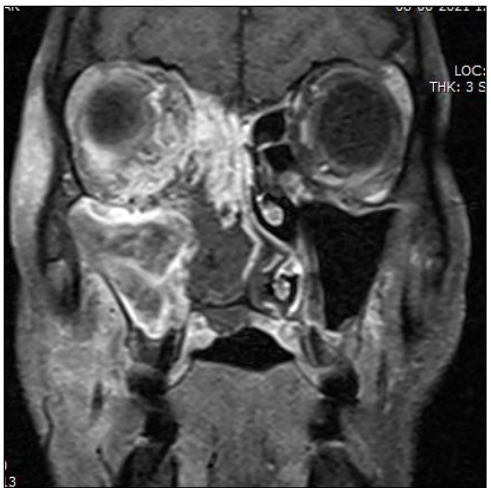


**Fig 7:A case of stage II RCM with orbital cellulitis, Coronal post contrast T1 FS image showing non enhancing mucosa of right middle and inferior turbinate -S/o Black turbinate sign**

**Case 02:**

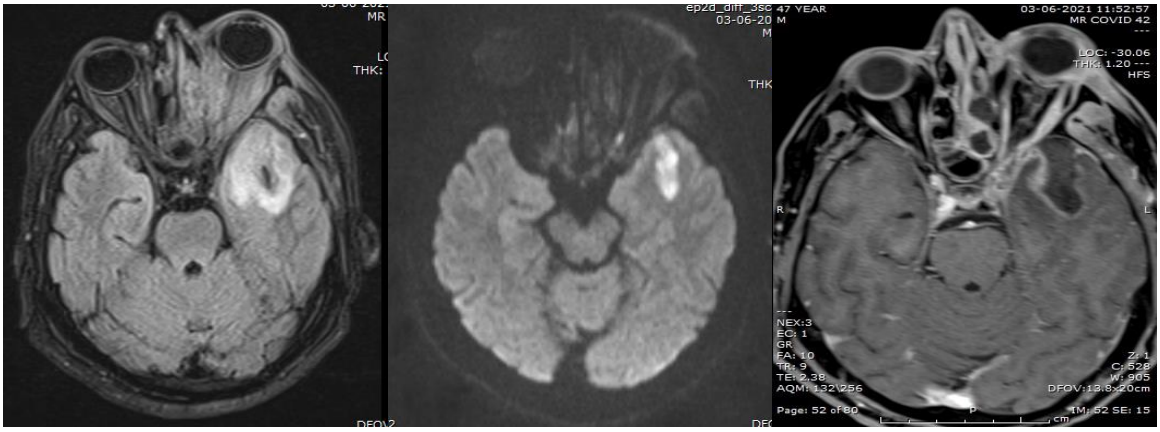
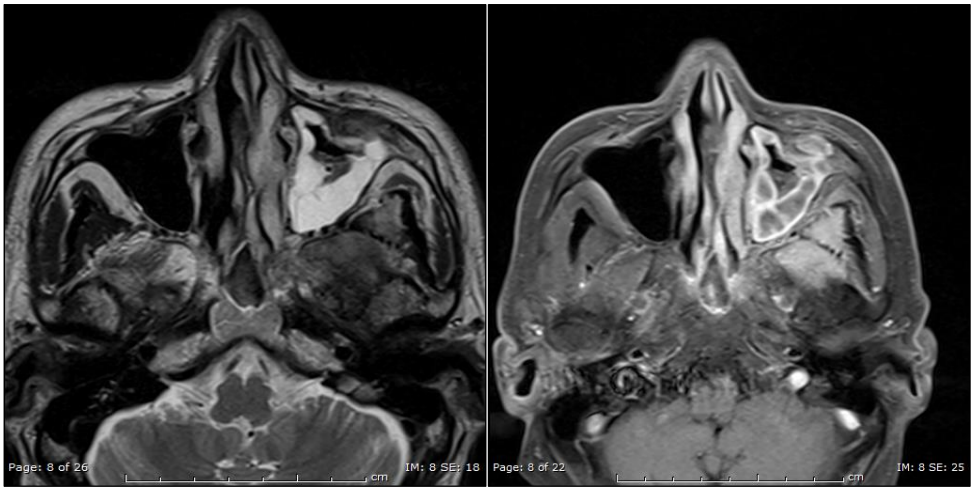


**Fig 8: A case of Left orbital cellulitis with `GUITAR PICK` sign, optic neuritis and intracranial involvement in the form of cerebral abscess in the left temporal lobe with focal pachymeningitis**

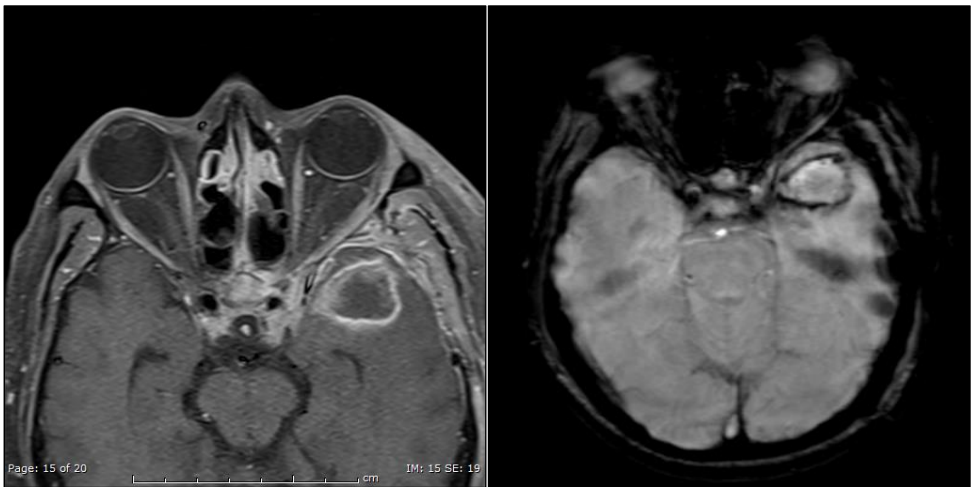
**Case 03:**



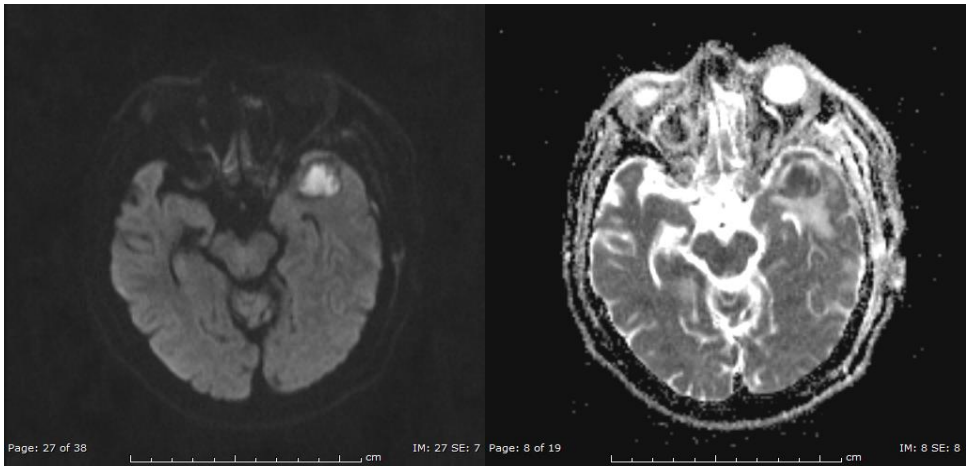
**(A)** **(B)**

**Fig 9: A case of STAGE III RCM, a- axial T2W image showing hyper-intense mucosal thickening in the left maxillary sinus. b- Post contrast T1 FS axial image showing inflammation in left masticator space**

**Case 04:**



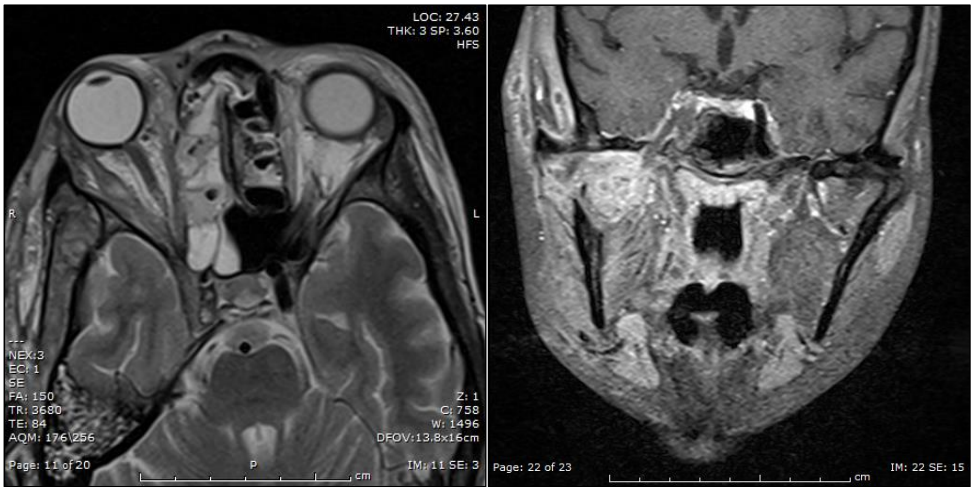
**(A)** **(B)**




**(C) (D)**

**Fig 10: A case of STAGE III RCM with fungal abscess , a-axial Post contrast T1FS image showing peripherally enhancing lesion in the left anterior temporal lobe, which on SWI (Image-b)showing peripheral blooming and on DWI and ADC (c,d) showing peripheral restriction**

**Case 05:**




**(A) (B)**

**Fig 11: 65year old diabetic female with mucormycosis. a. Axial T2 weighted image shows mucosal thickening in ethmoid and sphenoid sinuses. b. Coronal post contrast T1 FS image shows filling defect in right cavernous sinus-S/o cavernous sinus thrombosis**

## DISCUSSION

In our study, out of 72 patients affected with Covid-19 associated Rhinocerebral Mucormycosis, 72.2% are males and 27.8% are females. Males are more frequently affected compared to females which is similar to the study conducted by Herrera DA *et al.*[8] Mean age was 46.5 years. In our study most of the patients had comorbidities, among which the Diabetes being the predominant comorbidity. A study by Dubey*et al.* [9], all of the patients diagnosed with COVID-19 associated rhinocerebral mucormycosis were diabetics, which also included new-onset diabetes due to the usage of corticosteroids during the treatment of COVID-19.

History of steroid intake and oxygen supplementation was present in 7 patients (9%) and 19 patients (8.3%) respectively.

The invasion in mucormycosis has been divided into three stages as per Rupa*et al.* [7] In our study 6 patients were diagnosed with stage I disease with isolated sino-nasal involvement, 14 patients in stage II disease with sino-nasal-orbital involvement and 52 patients in stage III disease with intracranial involvement.

The disease spread in Covid-19 associated Rhinocerebral Mucormycosis based on anatomic involvement is classified as sinonasal, perisinus, orbital and intracranial disease.

## SINO NASAL AND PERISINUS DISEASE

The characteristic findings of early Sino nasal infection on MRI includes T2 hypo intensity, lack of mucosal enhancement which has been described as `black turbinate sign` and diffusion restriction. The above findings represent devitalised tissue and T2

hypo intensity is due to presence of fungal hyphae [10,11]. The T2 hypointesity is due to high concentration of iron and manganese in the fungal mass[12].Due to the angioinvasive propensity of mucormyosis and its ability to spread along the perineural and perivascular channels, the extra sinus extension can occur without frank bony destruction which, is the hallmark of Covid 19 associated mucormycosis[13].

Preantral and retroantral fat, infratemporal fossa, buccal space, masticator space, palate and oral cavity, sphenopalatine foramen and nasopharynx should be evaluated for disease spread. The infection may progress from obliteration of fat planes, stranding and inflammatory edema to abscess formation, osteomyelitis with cortical erosions and oroantral/oronasal fistula in advanced disease [14,15].

Black turbinate sign was seen in 23 patients among which 12 showed involvement of middle turbinate and11 patients showed involvement of inferior turbinate. In our study group, the most frequently affected para-nasal sinus was maxillary sinus followed by ethmoid, sphenoid and frontal sinus. In most of the patients multiple sinus involvement was seen. In a study conducted by safder*et al*.[11] Middle turbinate is the commonest site of involvement in the nasal cavity while maxillary, ethmoid and sphenoid sinuses are the commonly affected para-nasal sinuses[11].

## ORBITAL DISEASE

The spread of infection to the orbit occurs via infra-orbital foramen, inferior orbital fissure, and nasolacrimal duct along the inferior aspect of orbit, anterior and posterior ethmoidal foramen along the medial wall of orbit [16].

Due to orbital invasion and raised intra-orbital pressure secondary to inflammatory changes in the retro-orbital fat and orbital apex, which may results in proptosis. Involvement of extra-ocular muscles is evidenced by muscle thickening, displacement and abnormal enhancement on post contrast study[17]. Optic neuritis appears as thickening and enhancement of the optic nerve sheath"Guitar-Pick" sign which is a conical deformation of the posterior aspect of the ocular globe and Uveoscleral thickening which, are due to severely raised intra-orbital pressure (orbital compartmental syndrome)[18].

In our study the most common finding with orbital involvement was inflammation of the extra conal fat which was seen in 59% of patients followed by optic neuritis which was seen in 31% of patients. Involvement of extra ocular muscles was seen in 26% of patients, among which the most commonly involved extra-ocular muscle was medial rectus muscle. Similar to the study conducted by tharuna*et al*.[18]. Among the extra-ocular muscles, the first involved one is superior oblique muscle and medial rectus muscle due to its close proximity to the anterior ethmoidal foramen. Fat stranding in the intra and extra-conal compartments suggesting inflammation among which the inferior and medial extra-conal fat along with involvement of lacrimal sac were the early signs of orbital disease. Optic nerve showing restriction on DWI can be secondary to the invasion of the ophthalmic artery at the orbital apex or the optic canal, which is a predictor of irreversible loss of vision[19].Optic neuritis appears as enhancement and thickening of the optic nerve sheath[20].Other complications such as cellulitis, subperiosteal abscess, or orbital abscess can be assessed by standard MRI protocols with T1W, fat-saturated T2W, DWI, and postcontrast imaging[21].

## INTRACRANIAL DISEASE

Intracranial spread of the fungus can occurs by following ways: cribriform plate of ethmoid, orbital apex, angioinvasion and perineural spread, across the bony walls of frontal and sphenoid sinuses[22].Table 7 and Figure 6, summarizes the frequencies of various intra cranial complications. Among the various intracranial complications the most frequent complication was meningitis (23%) followed by infarcts (19%). Other intracranial complications were cavernous sinus thrombosis, internal carotid artery thrombosis, cerebritis, cerebral abscesses, extra axial collections and neuritis and nerve abscesses. Signs of cavernous sinus thrombosis includes, convexity of lateral wall of cavernous sinus, prominent superior ophthalmic vein and filling defect within the sinus.

In a retrospective study conducted by ashour*et al*.from May 2020 to February 2021, a total of 8 patients confirmed with COVID-19 infections presented with features of acute invasive fungal sinusitis. Variable imaging features were observed such as panophtalmitis, cavernous sinus thrombosis, vasculitis of the internal carotid artery and acute watershed infarcts[23].

In a case series of 10 patients by Mishra et al. it was proposed that patients with COVID-19 were susceptible to coinfection by mucormycosis due to impairment of the barrier defense, dysfunction of the phagocytes and lymphocytes and use of immunosuppressive drugs such as steroids and tocilizumab[24].

Chan *et al*. reported a case of skull base osteomyelitis and bony involvement from sinonasalmucormycosis in a 55 year old man under treatment for relapse of B cell chronic lymphocytic leukemia[25].

## CONCLUSION

MRI plays an important role in evaluating the extent of disease, various complications and pathologies to be searched in a case of ROCM, its aggressive management and timely intervention. Early diagnosis of invasive fungal rhino-sinusitis can enable optimal antimicrobial and surgical management, thus helps in reducing the morbidity and mortality of patients. Imaging techniques show only mucosal thickening in the early stage of the disease which may delay the

diagnosis. Hence high clinical suspicion is mandatory for picking up this condition.

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